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Applicant(s): Yogesh S. Sanghvi, et al.

Title: GAPPED OLIGOMERS HAVING SITE SPECIFIC CHIRAL

PHOSPHOROTHIOATE INTERNUCLEOSHIE LENKAGES

Serial No.: 09/438,989

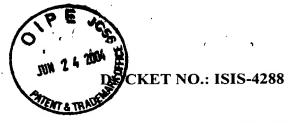
Filed: November 12, 1999

Docket No.: ISIS-4288

Date Sent: July 31, 2000

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

Yogesh S. Sanghvi et al.

Serial No.: 09/438,989

Group Art Unit: 1623

Filing Date: November 12, 1999

Examiner: Not Yet Assigned

For: GAPPED OLIGOMERS HAVING SITE SPECIFIC CHIRAL PHOSPHOROTHIOATE INTERNUCLEOSIDE LINKAGES

Date of deposit: July 31,2000

Date of deposit: <u>JUI SI, ZUI</u> I Hereby certify that this paper is being deposited with the United States Postal Service as First Class Mail, postage prepaid on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, DC 20231.

yped Name: Gwilym J.O. Attwell

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Assistant Commissioner for Patents Washington DC 20231

Dear Sir:

INFORMATION DISCLOSURE STATEMENT

Pursuant to 37 C.F.R. §1.56 and in accordance with 37 C.F.R. §§1.97-1.98, information relating to the above-identified application is hereby disclosed. Inclusion of information in this statement is not to be construed as an admission that this information is material as that term is defined in 37 C.F.R. §1.56(b).

In accordance with §1.97(b), since this Information Disclosure Statement is being filed either within three months of the filing date of the above-identified application, within three months of the date of entry into the national stage of the above identified application as set forth in §1.491, or before the mailing date of a first Office Action on the merits of the above-identified application, no additional fee is required.

 \boxtimes

	In acco	ordance with §1.129(a), this Information Disclosure Statement is being filed in
	connec	etion with □the first or □second After Final Submission, therefore:
		Certification in Accordance with §1.97(e) is attached; or
		The fee of \$240.00 as set forth in §1.17(p) is attached.
	In acco	ordance with §1.97(c), this Information Disclosure Statement is being filed
	after t	he period set forth in §1.97(b) above but before the mailing date of either
	a Fina	l Action under §1.113 or a Notice of Allowance under §1.311, therefore:
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	Copie	s of each of the references listed on the attached Form PTO-1449 are
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	EXC	EPT THAT:
	\boxtimes	In view of the voluminous nature of references CE-CG, and the likelihood that
	•	these references were available to the Examiner, copies were not enclosed in
		application Serial No. 09/115,027; A copy of reference CG was not enclosed in
		application Serial No. 09/352,058. A copies of references FI and FJ are not
		enclosed herewith.

- Pursuant to 37 C.F.R. 1.98(a)(2)(iii), no copy of a U.S. patent application

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- In accordance with §1.98(d), copies of the following references listed on the attached Form PTO-1449 are not enclosed herewith because they were previously cited by or submitted to the U.S. Patent and Trademark Office in patent application(s) for which a claim for priority under 35 U.S.C.§120 have been made in the instant application:
- Copies of references AA-CG, FK-FU, GA-GJ, GP-GY listed on the attached Form PTO-1449 were previously cited by or submitted to the Patent and Trademark Office in prior application Serial No. 09/115,027, filed July 14, 1998; and copies of references CH-EH, FV, and HE-JH listed on the attached Form PTO-1449 were previously cited by or submitted to the Patent and Trademark Office in prior application Serial No. 09/352,058, filed July 14, 1999.
 - ☐ If any of the foregoing publications are not available to the Examiner, Applicant will endeavor to supply copies at the Examiner's request.

Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050. This form is submitted in duplicate.

There are no listed references which are not in the English language.

Date: July 31, 2000

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MATERIAL PARTY	Form	PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989		
	(Patent and Publications Cited by Applicant everal sheets if necessary)	Applicant Yogesh S. Sanghvi, et al.			
		epartment of Commerce t and Trademark Office	Filing Date November 12, 1999	Group 1623		
	ОТНЕ	R DOCUMENTS (Including Author	r, Title, Date, Pertine	nt Pages, Etc.)		
AA Albert, P.R. et al., "Antisense knockouts: molecular scalpels for the dissect signal transduction", <i>Trends Pharmacol. Sci.</i> , 1994 , <i>15</i> , 250-254						
	AB Berkow et al. (eds.), <i>The Merck Manual of Diagnosis and Therapy</i> , Rahway, N.J. 1987, 15th Edition, 2263-2277, 2283-2292, 2301-2310			Therapy, Rahway, N.J.,		
AC Bernhard et al., "Direct Evidence Linking Expression of Matrix Metallops (92-kDa gelatinase/collagenase) to the metastatic phenotype in transforme embryo cells," <i>Proc. Natl. Acad. Sci. USA</i> , 1994 , <i>91</i> , 4293-4297				e in transformed rat		
	AD	Birkedal-Hansen, "Proteolytic Remodeling of Extracellular Matrix," Curr. Op. Cell Biol., 1995, 7, 728-735				
AE Boggemeyer et al., "Borrelia Burgdorferi Upregulates the Adhe selectin, P-selectin, ICAM-1 and VCAM-1 on Mouse Endothel Cell Adhes. Commun., 1994, 2, 145-157				Adhesion Molecules E- othelioma Cells in vitro,"		
	AF Cook, P.D., "Medicinal chemistry of antisense oligonucleotides - future opportunities", Anti-Cancer Drug Design, 1991, 6, 585-607					
AG Crooke, S.T. et al., "Pharmacokinetic Properties of Several Novel Oligonu Analogs in mice", J. Pharmacol. Exp. Therapeutics, 1996, 277, 923-937 AH Crooke, S.T. et al., "Progress in Antisense Oligonucleotide Therapeutic", Pharmacol. Toxicol., 1996, 36, 107-129				Novel Oligonucleotide 277, 923-937		
				Therapeutic", Ann. Rev.		
	AI	Dean, N.M. et al., "Inhibition of protein kinase C-α expression in mice after systemic administration of phosphorthioate antisense oligodeoxynucleotides", <i>Proc. Natl. Acad. Sci.</i> , 1994 , <i>91</i> , 11762-11766				
	AJ	DeLisser et al.,"Molecular and Func Today, 1994, 15(10), 490-494	tional Aspects of PEC	AM-1/CD31," Immunol.		
EXAMIN	ER		DATE CONSIDER	RED		

Form	PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989	
	f Patent and Publications Cited by Applicant everal sheets if necessary)	Applicant Yogesh S. Sanghvi et al.		
	Department of Commerce and Trademark Office	Filing Date November 12, 1999	Group 1623	
ОТНЕ	R DOCUMENTS (Including Autho	r, Title, Date, Pertine	nt Pages, Etc.)	
AK	Dimock et al., "An efficient multigrand novel oligonucleotides containing is & Nucleotides, 1997, 16(7-9), 1629-	osteric non-phosphorou		
AL	Downward, "The ras Superfamily of Small GTP-binding proteins," TIBS, 15, 1 469-472			
AM	Englisch, U. et al., "Chemically Mod Angew. Chem. Int. Ed. Eng., 1991, 3	Modified Oligonucleotides as Probes and Inhibitors", 91 , <i>30</i> , 613-629		
AN	Griffiths, C.E.M. et al., "Keratinocyte Intercellular Adhesion Molecule-1 (ICA Expression Precedes Derman T Lymphocyte Infiltration in Allergic Contact Dermatitis (<i>Rhus dermatitis</i>)", <i>Am. J. Pathology.</i> , 1989 , <i>135</i> , 1045-1053			
AO	Gum et al., "Stimulation of 92-kDa Gelatinase B Promoter Activity by ras Is Mitogen-activated Protein Kinase Kinase 1-independent and Requires Multiple Transcription Factor Binding Sites Including Closely Spaced PEA3/ets and AP-1 Sequences," J. Biol. Chem., 1996, 271(18), 10672-10680			
AP	Guzaev et al., "Synthesis of ¹⁴ C-Radiolabeled Oligonucleotides with a Novel Phosphoramidite Reagent", <i>Bioorg. Med. Chem. Lett.</i> , 1998 , <i>8</i> , 1123-1126			
AQ	AQ Hakugawa et al., "The Inhibitory Effect of Anti-Adhesion Molecule Antibodie Eosinophil Infilration in Cutaneous Late Phase Response in Balb/c Mice Sensi with Ovalbumin (OVA)," J. Dermatol., 1997, 24, 73-79			
AR	Hegemann, L. et al., "Biochemical Pharmacology of Protein Kinase C and its Relevance for Dermatology", <i>Pharmacology of the Skin</i> , Mukhtar, H. (ed.), CRC Press, Boca Raton, 1992 , <i>Ch.22</i> , 357-268			
AS	Himelstein et al., "Metalloproteinases in Tumor Progression: The Contribution of MMP-9," Invasion & Metastasis, 1994-95, 14, 246-258			
AT	Ho, V.C. et al., "Treatment of severe lichen planus with cyclosporine", J. Am. Acad. Dermatol., 1990, 22, 64-68			
EXAMINER		DATE CONSIDE	RED	



Form PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989	
List of Patent and Publications Cited by Applicant (Use several sheets if necessary)	Applicant Yogesh S. Sanghvi et al.		
U.S. Department of Commerce Patent and Trademark Office	Filing Date November 12, 1999	Group 1623	
OTHER DOCUMENTS (Including Author	or, Title, Date, Pertin	nent Pages, Etc.)	
AU Hua et al., "Inhibition of Matrix Me Blocks Metastasis in a Rat Sarcoma 5284			
Tissue Destruction in Scid Mice Inf	Hurtenback et al., "Prednisolone Reduces Experimental Arthritis and Inflammatory Tissue Destruction in Scid Mice Infected with Borrelia Burgdorferi," <i>Int. J. Immunopharmac</i> , 1996 , <i>18</i> (5), 281-288		
Oligodeoxyribonucleotides Using 3	Oligodeoxyribonucleotides Using 3H-1,2-Benzodithiol-3-one 1,1-Dioxide as a Sulfur-Transfer Reagent", J. Org. Chem., 1990, 55, 4693-4699		
hydrophobic substituent effectively			
	et al., "Biological Testing", Remington's Pharmaceutical Sciences, 18th (ed.), Mack Publishing Co., Easton, PA, 1990, Ch. 27, 484-494		
	AZ Kerr et al., "Growth Factors Regulate Transin Gene Expression by c-fos-Dependent and c-fos-Independent Pathways," Science, 1988, 242, 1424-1427		
BA Kerr et al., "TGF-\(\beta\)1 Inhibition of Transin/Stromelysin Gene Expression Is Media Through a Fos Binding Sequence," Cell, 1990, 61, 267-278			
BB Kroschwitz, J.I., "Polynucleotides" Engineering, 1990, John Wiley &	, Concise Encyclopedia of Polymer Science and Sons, New York, 858-859		
and activity as inhibitors of replication	BC Letsinger, R.L. et al., "Cholesteryl-conjugated oligonucleotides: Synthesis, proper and activity as inhibitors of replication of human immunodeficiency virus in cell culture", <i>Proc. Natl. Acad. Sci.</i> , 1989 , <i>86</i> , 6553-6556		
BD Lisby, S. et al., "Intercellular adhesinflammation", Br. J. Dermatol., 19		M-1) expression correlated to	
EXAMINER	DATE CONSIDI	ERED	

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TE TRADENA	Form	PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989	
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		epartment of Commerce t and Trademark Office	Filing Date November 12, 1999	Group 1623	
	OTHE	R DOCUMENTS (Including Author	r, Title, Date, Pertine	nt Pages, Etc.)	
	BE	Litwin et al., "Novel Cytokine-independent Molecules Regulated by Platelet/End Cell Biol., 1997, 139(1), 219-228	endent Induction of Er lothelial Cell Adhesion	ndothelial Adhesion Molecule (CD31)," J.	
	BF	Manoharan, M. et al., "Lipidic Nucleic Acids", Tetrahedron Letts., 1995, 36, 36, 3654			
	BG	Manoharan M. et al., "Cholic Acid-Oligonucliotide Conjugates for Antisen Applications", <i>Bioorganic Med. Chem. Letts.</i> , 1994 , <i>4</i> , 1053-1060			
	ВН	Manoharan, M. et al., "Introduction of Groove of Nucleic Acids for Antisen 1993, 3, 2765-2770	al., "Introduction of a Lipophilic Thioether Tether in the Minor Acids for Antisense Applications", <i>Bioorg. Med. Chem. Letts.</i> , 0		
	BI	Manoharan, M. et al., "Chemical Modifications to Improve Uptake and Bioavailability of Antisense Oligonucleotides", Annals NY Acad. Sciences, 1992 660, 306-309			
	ВЈ	Manoharan M. et al., "Oligonucleotic Properties of Antisense Agents", Nu	le Conjugates: Alterati cleosides and Nucleoti	on of the Pharmacokinetic ides, 1995, 14, 969-973	
	BK Martin, P., "Ein neuer Zugang zu 2'-O-Alkylribonucleosiden und Eigen Oligonucleotide", Helvetica Chemica Acta, 1995, 78, 486-504				
	BL	Mishra, R.K. et al., "Improved leishmanicidal effect of phosphorotioate antisense oligonucleotides by LDL-medicated delivery", <i>Biochim. Et Biophysica</i> , 1995 , <i>126</i> 229-237			
	ВМ	Newman, "Perspective Series: Cell A PECAM-1, J. Clin. Invest., 1997, 99		Biology," The Biology of	
	BN Nies, A.S. et al., "Principles of Therapeutics", Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., Hardman et al. (eds.), McGraw-F New York, NY, 1996, Ch. 3, 43-62				
EXAMIN	VER		DATE CONSIDE	RED	

	Sheet 5 of 26		
Form PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989	
List of Patent and Publications Cited by Applicant (Use several sheets if necessary)	Applicant Yogesh S. Sanghvi	et al.	
U.S. Department of Commerce Patent and Trademark Office	Filing Date November 12, 1999	Group 1623	
OTHER DOCUMENTS (Including Auth	or, Title, Date, Pertin	ent Pages, Etc.)	
BO Oberhauser, B. et al., "Effective in liposomes and enhanced cell assoc Nucl. Acids Res., 1992, 20, 533-53	iation through modifica		
	Regezi et al., "Vascular adhesion molecules in oral lichen planus", Oral Su Med. Oral Pathol., 1996, 81, 682-690		
BQ Ruoslahti, "How Cancer Spreads,"	Sci. Am., 1996, 72-77		
BR Saison-Behmoaras, T. et al., "Shor against Ha-ras point mutation inducells proliferation", EMBO J., 199	ice selective cleavage of	gonucleotides directed fthe mRNA and inhibit T24	
BS Sanghvi et al., "Concept, Discover Novel Linkage for Antisense Cons 907-916	Sanghvi et al., "Concept, Discovery and Development of MMI Linkage: Story of Novel Linkage for Antisense Constructs", Nucleosides & Nucleotides, 1997, 16 907-916		
Applications in Antisense Oligonu	Sanghvi, Y.S., "Heterocyclic Base Modifications in Nucleic acids and their Applications in Antisense Oligonucleotides", <i>Antisense Research and Applications</i> , Crooke et al. (Eds.), CRC Press, Boca Raton, 1993 , <i>Chapter 15</i> , 273-288		
BU Secrist, J.A. et al., "Synthesis and International Rountable: Nucleosi Sept. 16-20 1992, Abstact 21, Par.	des, Nucleotides and the	'-Thionucleosides", 10th eir Biological Applications,	
BV Shea, R.G. et al., "Synthesis, hybroligodeoxynucletide conjugates",	dization properties and antiviral activity of lipid- Nucl. Acids Res., 1990, 18, 3777-3783		
BW Shiohara et al., "Fixed drug Erupt Intercellular Adhesion Molecule-1 1376	Intercellular Adhesion Molecule-1 (ICAM-1)", Arch. Dermatol., 1989, 125, 137		
	During Invasion and Metastasis," Annu. Rev. Cell Biol., Palade, G.E. et al. (eds.),		
EXAMINER	DATE CONSIDE	RED	

Sheet 6 of 26

WE TRAUS	Form	PTO-1449 Modified	Docket No.	Serial No.
	List of	f Patent and Publications Cited by Applicant everal sheets if necessary)	Applicant Yogesh S. Sanghvi	09/438,989 et al.
		Department of Commerce at and Trademark Office	Filing Date November 12, 1999	Group 1623
_	ОТНЕ	ER DOCUMENTS (Including Author	r, Title, Date, Pertine	nt Pages, Etc.)
	BY	Svinarchuk, F.P. et al., "Inhibition of oligonucleotide conjugated to lipoph		
	BZ	Swayze et al., "The Synthesis of N,N'-O-Trisubstituted Hydroxylamines via a N Reductive Alkylation Procedure: An Improved Synthesis of the MMI Backbone Synlett, 1997, 859-861		
	CA	Swayze et al., "The Synthesis of the Sixteen Possible 2'-O-Methyl MMI I Phosphoramidites: Building Blocks for the Synthesis of Novel Antisense Oligonucleotides", <i>Nucleosides & Nucleotides</i> , 1997 , <i>16</i> (7-9), 971-972		
	СВ	U.S. Congress, Office of Technology Screening", <i>Genetic Monitoring and</i> Government Printing Office, Washir	Screening in the Work	kplace, OTA-BA-455, U.S.
	CC	Wahlestedt, C. et al., "Antisense olig channel protect cortical neurons from infarctions", <i>Nature</i> , 1993 , <i>363</i> , 260	n excitotoxicity and re	NMDA-R1 receptor duce focal ischaemic
	CD	Wahlestedt, C. et al., "Modulation of Antisense Oligodeoxynucleotides",		
*	CE	Ausubel, F.M. et al. (Eds.), Current Protocols in Molecular Biology, Current Publications, 1993		
*	CF	Sambrook, J. et al. (Eds.), <i>Molecular Cloning, A Laboratory Manual</i> , Second Ed., Cold Spring Harbor Laboratory Press, 1989		
*	CG	Green and Wuts, Protective Groups in Organic Synthesis, 2d edition, John Wiley & Sons, New York, 1991		
EXAM	INER		DATE CONSIDER	RED

^{*}A copy of this reference was not be forwarded to the U.S. Patent and Trademark Office since it was believed to be too voluminous and easily obtainable by the Examiner.

		Sheet / of 26		
Form PT	O-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989	
Cited	ent and Publications by Applicant l sheets if necessary)	Applicant Yogesh S. Sanghvi	et al.	
	tment of Commerce I Trademark Office	Filing Date November 12, 1999	Group 1623	
OTHER D	OCUMENTS (Including Author	r, Title, Date, Pertine	nt Pages, Etc.)	
Oli	rawal et al. (eds.), "Methods of Magonucleotide Conjugates, Agrawa 1-72			
	Alul, R.H. et al., "Oxalyl-CPG: a labile support for synthesis of sensitive oligonucleotide derivatives", <i>Nucl. Acid Res.</i> , 1991 , <i>19</i> , 1527-1532			
	chelin et al., "Structure of a stereo t. Struct. Biol., 1998, 5(4), 271-27		ate DNA/RNA duplex,"	
Mo Ini	Baker, B.F. et al., "2'-O-(2-Methoxy)ethyl-modified Anti-intercellular Adhesion Molecule 1 (ICAM-1) Oligonucleotides Selectively Increase the ICAM-1 Translation Complex in Human Umbilical Vein Endothelial Cells", <i>J. Biol. Chem.</i> , 1997, 272, 11994-12000			
CL Be	Beaucage, S.L. et al., "Advances in the Synthesis of Oligonucleotides by the Phosphoramidite Approach", <i>Tetrahedron</i> , 1992 , 48, 2223-2311			
	own, T. et al., "A New Base-stable others of the sis," J. Chem. Soc. Chem. Co.		se Oligonucleotide	
l Es	CN Burgers, P.M.J. et al., "A Study of the Mechanism of DNA Polymerase I from Escherichia coli with Diastereomeric Phosphorothioate Analogs of Deoxyadenosia Triphosphate", J. Biol. Chem., 1979, 254, 6889-6893			
CO Cr va	Crooke, S.T. et al., "Kinetic characteristics of <i>Escherichia coli</i> RNase H1: cleavage various antisense oligonucleotide-RNA duplexes", <i>Biochem. J.</i> , 1995 , <i>312</i> , 599-608			
gla	Damha, M.J. et al., "An improved procedure for derivatization of controlled-pore glass beads for solid-phase oligonucleotide synthesis", <i>Nucl. Acids Res.</i> , 1990 , <i>18</i> , 3813-3821			
	elgado, C. et al., "The Uses and Properties of the Properties of t		ed Proteins", Crit. Rev. in	
EXAMINER		DATE CONSIDE	RED	

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Form Form	PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989	
(Patent and Publications Cited by Applicant everal sheets if necessary)	Applicant Yogesh S. Sanghvi et al.		
	Filing Date Group and Trademark Office November 12, 1999			
ОТНЕ	R DOCUMENTS (Including Author	r, Title, Date, Pertine	nt Pages, Etc.)	
CR	Efimov, V.A. et al., "New efficient sulfu oligodeoxyribonucleotide phosphorothioate			
CS	Eliel, E.L. et al., "Asymmetric Synth Reaction," J. Am. Chem. Soc., 1984,		thianes. 1. Scope of the	
СТ	Eliel, E.L. et al., "Neighboring Group γ-Alkoxy Substituted p-Toluenesulfonate	Participation by Oxygen tes," <i>J. Org. Chem.</i> , 19	in the Solvolysis of Acyclic 85 , <i>50</i> , 2707-2711	
CU	Eliel, E.L. et al., "Neighboring Group Membered-Ring Intermediates (RS-4			
CV	Eliel, E.L. et al., "Highly Stereoselective Syntheses Involving N-Alkyl-4,4,7α-trimethyl-trans-octahydro-1,3-benzoxazine Intermediates," J. Org. Chem., 1990, 55, 2114-2119			
CW	Eliel, E.L. et al., "Asymmetric Synthesis of (R)-(+)-Ethylmethyl-n-Propylcarbinol in High Enantiomeric Purity. A 1,3-Oxathiane Derived from (+)-Pulegone as Chiral Adjuvant," <i>Tetra Lett.</i> , 1981 , 22(30), 2855-2858			
CX	Froehler, B.C., "Oligodeoxynucleotic Protocols for Oligonucleotides and A (ed.), Humana Press, 1993, Ch. 4, 63	Analogs: Synthesis and	honate Approach," in I Properties, Agrawal S.	
СУ	Gait, M. J. ed., "An Introduction to It Oligonucleotide Synthesis, A Practic Press, Oxford, Ch. 1, 1-22	Modern Methods of Dical Approach, IRL Pres	NA Synthesis," ss, Oxford, 1985 , IRL	
CZ	Griffiths, A.D. et al., "Stereospecificity of nucleases towards phosphorothioate-substituted RNA: stereochemistry of transcription by T7 RNA polymerase," <i>Nucl. Acids Res.</i> , 1987, 15(10), 4145-4162			
DA	Hacia, J.G. et al., "Phosphorothioate Oligonucleotide-Directed Triple Helix Formation," <i>Biochem.</i> , 1994 , <i>33</i> , 5367-5369			
DB	Hamm, M. L. et al., "Incorporation of 2'-Deoxy-2'-mercaptocytidine into Oligonucleotide via Phosphoramidite Chemistry," J. Org. Chem., 1997, 62, 3415-3420			
DC	He, X-C. et al., "Highly Enantioselective Syntheses of α-Hydroxyacids Using N-Benzyl-4,4,7α-Trimethyl- <u>Trans</u> -Octahydro-1,3-Benzoxazine as a Chiral Adjuvant," <i>Tetrahedron</i> , 1987 , 43(21), 4979-4987			
EXAMINER		DATE CONSIDER	RED	

List of Patent and Publications Cited by Applicant (Use several sheets if necessary) U.S. Department of Commerce Patent and Trademark Office Patent and Trademark Office Dot Iyer, R.P. et al., "3H-1,2-Benzodithiole-3-one 1,1-Dioxide as an Improved Sulfurizin Reagent in the Solid-Phase Synthesis of Oligodeoxyribonucleoside Phosphorothioates", J. Am. Chem. Soc., 1990, 112, 1253-1254 DE Jin, Y. et al., "Stereoselective Synthesis of Dithymidine Phosphorothioates Using Xylose Derivatives as Chiral Auxiliaries," J. Org. Chem., 1998, 63, 3647-3654 DF Jung, M.E., "New Gem- and Vic-Disubstituent Effects on Cyclizations," Synlett, 199 S1, 843-846 DG Kamer, P.C.J. et al., "An Efficient Approach Toward the Synthesis of Phosphorothioate Diesters via the Schonberg Reaction", Tetrahedron Letts., 1989, 3 6757-6760 DH Koziolkiewicz, M. et al., "Stability of Stereoregular Oligo(nucleoside Phosphorothioates)s in Human Plasma: Diastereoselectivity of Plasma 3'-Exonuclease," Antisense Nucl. Acid Drug Dev., 1997, 7, 43-48 DI Koziolkiewicz, M. et al., "Stereodifferentiation – the effect of P chirality of oligo(nucleoside phosphorothioates) on the activity of bacterial RNase H," Nucl. Acids Res., 1995, 23(24), 5000-5005 DJ Koziolkiewicz, M. et al., "Enzymatic Assignment of Diastereomeric Purity of Stereodefined Phosphorothioate Oligonucleotides," Antisense Nucl. Acid Drug Dev. 1999, 9, 171-181 DK Koziolkiewicz, M. et al., "Stability of Stereoregular Oligo(nucleoside	1 5 t my E			Sheet 9 of 26		
Cited by Applicant (Use several sheets if necessary) U.S. Department of Commerce Patent and Trademark Office Patent and Trademark Office OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) DD Iyer, R.P. et al., "3H-1,2-Benzodithiole-3-one 1,1-Dioxide as an Improved Sulfurizin Reagent in the Solid-Phase Synthesis of Oligodeoxyribonucleoside Phosphorothioates", J. Am. Chem. Soc., 1990, 112, 1253-1254 DE Jin, Y. et al., "Stereoselective Synthesis of Dithymidine Phosphorothioates Using Xylose Derivatives as Chiral Auxiliaries," J. Org. Chem., 1998, 63, 3647-3654 DF Jung, M.E., "New Gem- and Vic-Disubstituent Effects on Cyclizations," Synlett, 1995, 18, 843-846 DG Kamer, P.C.J. et al., "An Efficient Approach Toward the Synthesis of Phosphorothioate Diesters via the Schonberg Reaction", Tetrahedron Letts., 1989, 3 6757-6760 DH Koziolkiewicz, M. et al., "Stability of Stereoregular Oligo(nucleoside Phosphorothioates) in Human Plasma: Diastereoselectivity of Plasma 3'-Exonuclease," Antisense Nucl. Acid Drug Dev., 1997, 7, 43-48 DI Koziolkiewicz, M. et al., "Stereodifferentiation - the effect of P chirality of oligo(nucleoside phosphorothioates) on the activity of bacterial RNase H," Nucl. Acids Res., 1995, 23(24), 5000-5005 DJ Koziolkiewicz, M. et al., "Enzymatic Assignment of Diastereomeric Purity of Stereodefined Phosphorothioate Oligonucleotides," Antisense Nucl. Acid Drug Dev. 1999, 9, 171-181	TA TRAILEMENT	Form	PTO-1449 Modified	1		
Patent and Trademark Office November 12, 1999 OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) DD Iyer, R.P. et al., "3H-1,2-Benzodithiole-3-one 1,1-Dioxide as an Improved Sulfurizin Reagent in the Solid-Phase Synthesis of Oligodeoxyribonucleoside Phosphorothioates", J. Am. Chem. Soc., 1990, 112, 1253-1254 DE Jin, Y. et al., "Stereoselective Synthesis of Dithymidine Phosphorothioates Using Xylose Derivatives as Chiral Auxiliaries," J. Org. Chem., 1998, 63, 3647-3654 DF Jung, M.E., "New Gem- and Vic-Disubstituent Effects on Cyclizations," Synlett, 199 S1, 843-846 DG Kamer, P.C.J. et al., "An Efficient Approach Toward the Synthesis of Phosphorothioate Diesters via the Schonberg Reaction", Tetrahedron Letts., 1989, 3 6757-6760 DH Koziolkiewicz, M. et al., "Stability of Stereoregular Oligo(nucleoside Phosphorothioate)s in Human Plasma: Diastereoselectivity of Plasma 3'-Exonuclease," Antisense Nucl. Acid Drug Dev., 1997, 7, 43-48 DI Koziolkiewicz, M. et al., "Stereodifferentiation – the effect of P chirality of oligo(nucleoside phosphorothioates) on the activity of bacterial RNase H," Nucl. Acid Res., 1995, 23(24), 5000-5005 DJ Koziolkiewicz, M. et al., "Enzymatic Assignment of Diastereomeric Purity of Stereodefined Phosphorothioate Oligonucleotides," Antisense Nucl. Acid Drug Dev. 1999, 9, 171-181			Cited by Applicant	1	et al.	
DD Iyer, R.P. et al., "3H-1,2-Benzodithiole-3-one 1,1-Dioxide as an Improved Sulfurizin Reagent in the Solid-Phase Synthesis of Oligodeoxyribonucleoside Phosphorothioates", J. Am. Chem. Soc., 1990, 112, 1253-1254 DE Jin, Y. et al., "Stereoselective Synthesis of Dithymidine Phosphorothioates Using Xylose Derivatives as Chiral Auxiliaries," J. Org. Chem., 1998, 63, 3647-3654 DF Jung, M.E., "New Gem- and Vic-Disubstituent Effects on Cyclizations," Synlett, 199 S1, 843-846 DG Kamer, P.C.J. et al., "An Efficient Approach Toward the Synthesis of Phosphorothioate Diesters via the Schonberg Reaction", Tetrahedron Letts., 1989, 3 6757-6760 DH Koziolkiewicz, M. et al., "Stability of Stereoregular Oligo(nucleoside Phosphorothioate)s in Human Plasma: Diastereoselectivity of Plasma 3'-Exonuclease," Antisense Nucl. Acid Drug Dev., 1997, 7, 43-48 DI Koziolkiewicz, M. et al., "Stereodifferentiation – the effect of P chirality of oligo(nucleoside phosphorothioates) on the activity of bacterial RNase H," Nucl. Acids Res., 1995, 23(24), 5000-5005 DJ Koziolkiewicz, M. et al., "Enzymatic Assignment of Diastereomeric Purity of Stereodefined Phosphorothioate Oligonucleotides," Antisense Nucl. Acid Drug Dev. 1999, 9, 171-181			•	November 12,	I =	
Reagent in the Solid-Phase Synthesis of Oligodeoxyribonucleoside Phosphorothioates", J. Am. Chem. Soc., 1990, 112, 1253-1254 DE Jin, Y. et al., "Stereoselective Synthesis of Dithymidine Phosphorothioates Using Xylose Derivatives as Chiral Auxiliaries," J. Org. Chem., 1998, 63, 3647-3654 DF Jung, M.E., "New Gem- and Vic-Disubstituent Effects on Cyclizations," Synlett, 199 S1, 843-846 DG Kamer, P.C.J. et al., "An Efficient Approach Toward the Synthesis of Phosphorothioate Diesters via the Schonberg Reaction", Tetrahedron Letts., 1989, 3 6757-6760 DH Koziolkiewicz, M. et al., "Stability of Stereoregular Oligo(nucleoside Phosphorothioate)s in Human Plasma: Diastereoselectivity of Plasma 3'-Exonuclease," Antisense Nucl. Acid Drug Dev., 1997, 7, 43-48 DI Koziolkiewicz, M. et al., "Stereodifferentiation – the effect of P chirality of oligo(nucleoside phosphorothioates) on the activity of bacterial RNase H," Nucl. Acids Res., 1995, 23(24), 5000-5005 DJ Koziolkiewicz, M. et al., "Enzymatic Assignment of Diastereomeric Purity of Stereodefined Phosphorothioate Oligonucleotides," Antisense Nucl. Acid Drug Dev., 1999, 9, 171-181		ОТНЕ	R DOCUMENTS (Including Autho	r, Title, Date, Pertino	ent Pages, Etc.)	
Xylose Derivatives as Chiral Auxiliaries," J. Org. Chem., 1998, 63, 3647-3654 DF Jung, M.E., "New Gem- and Vic-Disubstituent Effects on Cyclizations," Synlett, 199 \$1, 843-846 DG Kamer, P.C.J. et al., "An Efficient Approach Toward the Synthesis of Phosphorothioate Diesters via the Schonberg Reaction", Tetrahedron Letts., 1989, 3 6757-6760 DH Koziolkiewicz, M. et al., "Stability of Stereoregular Oligo(nucleoside Phosphorothioate)s in Human Plasma: Diastereoselectivity of Plasma 3'- Exonuclease," Antisense Nucl. Acid Drug Dev., 1997, 7, 43-48 DI Koziolkiewicz, M. et al., "Stereodifferentiation – the effect of P chirality of oligo(nucleoside phosphorothioates) on the activity of bacterial RNase H," Nucl. Acids Res., 1995, 23(24), 5000-5005 DJ Koziolkiewicz, M. et al., "Enzymatic Assignment of Diastereomeric Purity of Stereodefined Phosphorothioate Oligonucleotides," Antisense Nucl. Acid Drug Dev. 1999, 9, 171-181		DD	Reagent in the Solid-Phase Synthesis	s of Oligodeoxyribonu	ıcleoside	
DG Kamer, P.C.J. et al., "An Efficient Approach Toward the Synthesis of Phosphorothioate Diesters via the Schonberg Reaction", <i>Tetrahedron Letts.</i> , 1989, 3 6757-6760 DH Koziolkiewicz, M. et al., "Stability of Stereoregular Oligo(nucleoside Phosphorothioate)s in Human Plasma: Diastereoselectivity of Plasma 3'-Exonuclease," <i>Antisense Nucl. Acid Drug Dev.</i> , 1997, 7, 43-48 DI Koziolkiewicz, M. et al., "Stereodifferentiation – the effect of P chirality of oligo(nucleoside phosphorothioates) on the activity of bacterial RNase H," <i>Nucl. Acids Res.</i> , 1995, 23(24), 5000-5005 DJ Koziolkiewicz, M. et al., "Enzymatic Assignment of Diastereomeric Purity of Stereodefined Phosphorothioate Oligonucleotides," <i>Antisense Nucl. Acid Drug Dev.</i> 1999, 9, 171-181		DE	Jin, Y. et al., "Stereoselective Synthe Xylose Derivatives as Chiral Auxilia	esis of Dithymidine Phries," J. Org. Chem.,	nosphorothioates Using 1998, 63, 3647-3654	
Phosphorothioate Diesters via the Schonberg Reaction", Tetrahedron Letts., 1989, 3 6757-6760 DH Koziolkiewicz, M. et al., "Stability of Stereoregular Oligo(nucleoside Phosphorothioate)s in Human Plasma: Diastereoselectivity of Plasma 3'- Exonuclease," Antisense Nucl. Acid Drug Dev., 1997, 7, 43-48 DI Koziolkiewicz, M. et al., "Stereodifferentiation – the effect of P chirality of oligo(nucleoside phosphorothioates) on the activity of bacterial RNase H," Nucl. Acids Res., 1995, 23(24), 5000-5005 DJ Koziolkiewicz, M. et al., "Enzymatic Assignment of Diastereomeric Purity of Stereodefined Phosphorothioate Oligonucleotides," Antisense Nucl. Acid Drug Dev. 1999, 9, 171-181		DF	_	Disubstituent Effects on Cyclizations," Synlett, 1999,		
Phosphorothioate)s in Human Plasma: Diastereoselectivity of Plasma 3'- Exonuclease," Antisense Nucl. Acid Drug Dev., 1997, 7, 43-48 DI Koziolkiewicz, M. et al., "Stereodifferentiation - the effect of P chirality of oligo(nucleoside phosphorothioates) on the activity of bacterial RNase H," Nucl. Acids Res., 1995, 23(24), 5000-5005 DJ Koziolkiewicz, M. et al., "Enzymatic Assignment of Diastereomeric Purity of Stereodefined Phosphorothioate Oligonucleotides," Antisense Nucl. Acid Drug Dev. 1999, 9, 171-181		DG	Phosphorothioate Diesters via the Sc	Approach Toward the Synthesis of Schonberg Reaction", <i>Tetrahedron Letts.</i> , 1989 , <i>30</i> ,		
oligo(nucleoside phosphorothioates) on the activity of bacterial RNase H," <i>Nucl. Acids Res.</i> , 1995 , <i>23(24)</i> , 5000-5005 DJ Koziolkiewicz, M. et al., "Enzymatic Assignment of Diastereomeric Purity of Stereodefined Phosphorothioate Oligonucleotides," <i>Antisense Nucl. Acid Drug Dev.</i> 1999 , <i>9</i> , 171-181		DH	Phosphorothioate)s in Human Plasm	sma: Diastereoselectivity of Plasma 3'-		
Stereodefined Phosphorothioate Oligonucleotides," Antisense Nucl. Acid Drug Dev. 1999, 9, 171-181		DI	oligo(nucleoside phosphorothioates)	on the activity of bac	et of P chirality of eterial RNase H," Nucl.	
DV Voziolkiewicz M et al "Stability of Stereoregular Oligo(nucleoside		DJ	Stereodefined Phosphorothioate Olig			
phosphorothioate)s in Human Cells; Diastereoselectivity of Cellular 3'-Exonuclease Nucleosides & Nucleotides, 1997, 16(7-9), 1677-1682		DK	phosphorothioate)s in Human Cells;	ls; Diastereoselectivity of Cellular 3'-Exonuclease,"		
Lackey, D.B. et al., "Biochemical synthesis of chirally pure <i>Rp</i> oligonucleotide phosphorothioates," <i>Biotechnol. Lett.</i> , 1997 , <i>19(5)</i> , 475-478		DL				
Lima, W.F. et al., "Binding Affinity and Specificity of Escherichia coli Rnase H1: Impact on the Kinetics of Catalysis of Antisense Oligonucleotide-RNA Hybrids," Biochemistry, 1997, 36, 390-398		DM Lima, W.F. et al., "Binding Affinity and Specificity of Escherichia coli Rnase H1 Impact on the Kinetics of Catalysis of Antisense Oligonucleotide-RNA Hybrids,"				
EXAMINER DATE CONSIDERED	EXAMIN	ER		DATE CONSIDE	RED	

FAT & TRAILERS	Form	PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989	
,	C	Patent and Publications Cited by Applicant veral sheets if necessary)	Applicant Yogesh S. Sanghvi et al.		
		epartment of Commerce and Trademark Office	Filing Date November 12, 1999	Group 1623	
·	OTHE	R DOCUMENTS (Including Author	r, Title, Date, Pertine	nt Pages, Etc.)	
	Ludwig, J. et al., "Rapid and Efficient Synthesis of Nucleoside 5'-O-(1-Thiotriphosphates), 5'-Triphosphates and 2',3'-Cyclophosphorothioates Using 2'Chloro-4H-1,3,2-benzodioxaphosphorin-4-one", J. Org. Chem., 1989, 54, 631				
	DO	Lynch et al., "Asymmetric Syntheses Based on 1,3-Oxathianes. 2. Synthesis of Chiral Tertiar Hydroxy Aldehydes, α-Hydroxy Acids, Glycols (RR'C(OH)CH ₂ OH), and Carbinols (RR'C(OH) in High Enantiomeric Purity," <i>J. Am. Chem. Soc.</i> , 1984 , <i>106</i> , 2943-2948			
	DP	Minshull, J. et al., "The use of single-stranded DNA and RNase H to promote quantitative 'hybrid arrest of translation' of mRNA/DNA hybrids in reticulocyte lysate cell-free translations", <i>Nucl. Acids. Res.</i> , 1986 , <i>14</i> , 6433-6451			
	DQ	to 5'-Fluorouracil via a Urethane or Urea Bond", Drug Des. & Disc., 1992, 9, 9			
	DR				
	DS	Rao, M.V. et al., "Dibenzoyl Tetrası Synthesis of Phosphorothioate Analo 1992, 33, 4839-4842	asulphide-A Rapid Sulphur Transfer Agent in the alogues of Oligonucleotides", Tetrahedron Letts.,		
	DT	Ravasio, N. et al., "Selective Hydrogenations Promoted by Copper Catalysts. 1. Chemoselectivity, Regioselectivity, and Stereoselectivity in the Hydrogenation of 3-Substituted Steroids", J. Org. Chem., 1991, 56, 4329-4333			
	DU	Sierzchala, A. et al., "Oxathiaphospholane Method of Stereocontrolled Synthesis of Diribonucleoside 3',5'-Phosphorothioates," <i>J. Org. Chem.</i> , 1996 , <i>61</i> , 6713-6716			
	DV	Slim, G. et al., "Configurationally defined phosphorothioate-containing oligoribonucleotides in the study of the mechanism of cleavage of hammerhead ribozymes," <i>Nucl. Acids Res.</i> , 1991 , <i>19(6)</i> , 1183-1188			
	DW Stec, W.J. et al., "Deoxyribonucleoside 3'-O-(2-Thio- and 2-Oxo-"sprio"-4,4-pentamethylene-1,3,2-oxathiaphospholane)s: Monomers for Stereocontrolled Sy Oligo(deoxyribonucleoside phosphorothioate)s and Chimeric PS/PO Oligonucle Am. Chem. Soc., 1998, 120, 7156-7167				
EXAMIN	ER		DATE CONSIDE	RED	

OH 5 4 5000 E			Sheet 11 of 26	
Form Form	PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989	
	f Patent and Publications Cited by Applicant everal sheets if necessary)	Applicant Yogesh S. Sanghvi	et al.	
1	Department of Commerce at and Trademark Office	Filing Date November 12, 1999	Group 1623	
ОТНЕ	CR DOCUMENTS (Including Autho	or, Title, Date, Pertine	nt Pages, Etc.)	
DX	Stec, W.J. et al., "Stereocontrolled S phosphorothioate)s", Angew. Chem.			
DY	Stec, W.J. et al., "Bis (O,O-Diisopro Efficient Sulfurizing Reagent for Co Phosphorothioate)s", <i>Tetrahedron Letter</i>	st-Effective Synthesis	of Oligo(Nucleoside	
DZ	Stec, W.J. et al., "Diastereomers of Nucleoside 3'-O-(2-THio-1,3,2-ozathia(selena)phospholanes): Building Blocks for Stereocontrolled Synthesis of Oligo(nucleoside Phosphorothioate)s," J. Am. Chem. Soc., 1995, 117(49), 12019-120			
EA	Tang, J. et al., "Enzymatic Synthesis of Stereoregular (all Rp) Oligonucleotide Phosphorothioate and its Properties," <i>Nucleosides & Nucleotides</i> , 1995 , <i>14(3-5)</i> , 985-			
ЕВ	Thomson, J. B. et al., "Synthesis and Properties of Diuridine Phosphate Analogues Containing Thio and Amino Modifications," J. Org. Chem., 1996, 61, 6273-6281			
EC	Vu, H. et al, "Internucleotide Phosphite Sulfurization with Tetraethylthiuram Disulfide. Phosphorothioate Oligonucleotide Synthesis via Phosphoramidite Chemistry", <i>Tetrahedron Letts.</i> , 1991 , <i>32</i> , 3005-3008			
ED		ang, J.C. et al., "A Stereoselective Synthesis of Dinucleotide Phosphorothioate iesters through a Chiral Indol-oxazaphosphorine Intermediate," <i>Tetra. Lett.</i> , 1997 , (5), 705-708		
EE	Wang, J.C. et al., "A Stereoselective Chiral Indol-oxazaphosphorine Intermediate Chiral Indol-oxazaphosphorine Intermediate Chiral Indol-oxazaphosphorine Intermediate Chiral Indol-oxazaphosphorine Intermediate Chiral Ind			
EF	Wright, P. et al., "Large Scale Synthesis of Oligonucleotides via phosphoramidite Nucleosides and a High-loaded Polystyrene Support", <i>Tetrahedron Letts.</i> , 1993 , <i>34</i> , 3373-3376			
EG	EG Xu, Q. et al., "Efficient introduction of phosphorothioates into RNA oligonucleotic by 3-ethoxy-1,2,4-dithiazoline-5-one (EDITH)", Nucl. Acids Res., 1996, 24, 3643-3644			
ЕН	H Xu, Q. et al., "Use of 1,2,4-dithiazolidine (DtsNH) and 3-ethoxy-1,2,4-dithiazoline-5-one (EDITH) for synthesis of phosphorothioate-containing oligodeoxyribonucleotides", <i>Nucl. Acids Res.</i> , 1996 , <i>24</i> , 1602-1607			
EXAMINER		DATE CONSIDER	RED	

			Sneet 12 of 26	
Form Form	PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989	
	of Patent and Publications Cited by Applicant everal sheets if necessary)	Applicant Yogesh S. Sanghvi et al.		
	Department of Commerce nt and Trademark Office	Filing Date November 12, 1999	Group 1623	
ОТН	ER DOCUMENTS (Including Author	r, Title, Date, Pertine	nt Pages, Etc.)	
EI	Arnott, S. et al., "Optimised Paramet Biophys. Res. Comm., 1972, 47, 1504		DNA", Biochem. &	
EJ	Bryant, F.R., et al., "Phosphorothioa 1982, 21, 5877-5885	ite substrates for T4 R1	NA ligase," Biochem.,	
EK	Berkow et al. (eds.), <i>The Merck Man</i> Rahway, N.J., 1987 , 2286-2293	ual of Diagnosis and I	Therapy, 15th Edition,	
EL	Bhat, B. et al., "Synthesis of Novel Nucleic Acid Mimics via the Stereoselective Intermolecular Radical Coupling of 3'-Iodo Nucleosides and Formaldoximines", J. Org. Chem., 1996, 61, 8186-8199			
EM	Brennan et al., "NA ligase catalyzed synthesis of base analogue-containing oligodeonyribonucleotides and a characterization of their theral stabilities," <i>Nucl. Acids Res.</i> , 1985 , <i>13</i> , 8665-8684			
EN	Brennan et al., "[2] Using T4 RNA l 1983, 100, 38-53	igase with DNA substr	rates," Methods Enzymol.,	
EO	Connolly, in Oligonucleotides and A IRL Press, 1991, 155-183	nalogs: A Practical Ap	oproach, Eckstein, F. (ed.),	
EP	Coull, J.M., et al., "Synthesis and choligonucleoside," Tet. Lett., 1987, 28		oamate-linked	
EQ	Damha M.J., et al., "Antisense L/D-oligodeoxynucleotide chimeras: nuclease stability, based-pairing properties, and activity at directing ribonuclease H," Biochemistry, 1994, 33, 7877-7885			
ER	Eckstein, F., "Nucleoside Phosphorothioates", Ann. Rev. Biochem., 1985, 54, 36			
ES	Guo et al., "Solid-phase stereoselective synthesis of 2'-0-methyl-oligoribonucleoside phosphorothioates using nucleoside bicyclic oxazaphospholidines," <i>Bioorg. & Med. Chem. Lett.</i> , 1998 , <i>8</i> , 2539-2544			
EXAMINER		DATE CONSIDER	RED	

61	Eicse
NUL)	24 2004 副
377	74 TRAITEMENT
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EXAMIN	antisense oligonucleotides," in <i>Manuals of Antisense Technology</i> , Hartmann, G. et a (eds.), Kulver Press, 1999, 3, 3-23			nology, Hartmann, G. et al.
	FC	Sanghvi, Y.S., et al., "Chemical synt	-	
	FB	Reynolds, R.C. et al., "Synthesis of Thymidine Dimers Containing Internucleoside Sulfonate and Sulfonamide Linkages", J. Org. Chem., 1992, 57, 2983-2985		
	FA	Musichi, B., et al., "Synthesis of carbohydrate sulfonates and sulfonate esters," J. Org. Chem., 1990, 55(14), 4231-4233		
	EZ	Mungall, W.S. et al., "Carbamate An 1977 , <i>42</i> , 703-706		
	EY	Monia, B.P. et al., "Evaluation of 2'-M as Antisense Inhibitors of Gene Express		
	EX	Hewitt, J.M. et al., "Structural Determination of Silicon-Containing Oligonucleotides by ¹ H ⁻²⁹ Si Long-Range Heteronuclear Multiple Quantum Correlation NMR Spectroscopy", 1992 , <i>11</i> , 1661-1666		
	EW	McGall et al., "The efficiency of light-directed synthesis of DNA arrays on glass substrates," J. Am. Chem. Soc., 1997, 119, 5081-5090		
	EV	Kool, E. (ed.), in <i>Chemistry: DNA an</i> Press, 1999 , <i>Vol. 7</i> , 285-311	nd Aspects of Molecula	r Biology, Pergamon
	EU	King, D.J., et al., "Novel combinator aptamers," <i>Biochem.</i> , 1998, <i>37</i> , 1648		orothioate oligonucleotide
	ET	Hewitt, J.M. et al., "Structural Determine by ¹ H ⁻²⁹ Si Long-Range Heteronuclean Spectroscopy", 1992 , <i>11</i> , 1661-1666	r Multiple Quantum Co	
	ОТН	ER DOCUMENTS (Including Author	r, Title, Date, Pertinent	Pages, Etc.)
		epartment of Commerce t and Trademark Office	Filing Date November 12, 1999	Group 1623
	(Patent and Publications Cited by Applicant veral sheets if necessary)	Applicant Yogesh S. Sanghvi e	et al.
TA TRAUE MAN	Form	PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989

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Forn	n PTO-1449 Modified	Docket No. ISIS-4288	Serial No. 09/438,989	
	of Patent and Publications Cited by Applicant several sheets if necessary)	Applicant Yogesh S. Sanghvi et al.		
	Department of Commerce nt and Trademark Office	Filing Date November 12, 1999	Group 1623	
ОТН	ER DOCUMENTS (Including Auth	or, Title, Date, Perti	nent Pages, Etc.)	
FD	Sood, A. et al., "Boron-Containing Oligodeoxynucleoside Boranophos			
FE	Stirchak, E.P. et al., "Uncharged Stereoregular Nucleic Acid Analogs. I. Syr a Cytosine-Containing Oligomer with Carbamate Internucleoside Linkages", <i>Chem.</i> , 1987 , <i>52</i> , 4202-4206			
FF	Stirchak, E.P. et al., "Uncharged stereoregular nucleic acid analogs: 2. Morphol nucleoside oligomer with carbamate internucleoside linkages", <i>Nucl. Acids Res.</i> 1989 , <i>17</i> , 6129-6134			
FG	Vasseur, J.J. et al., "Oligonucleosides: Synthesis of a Novel Methylhydroxylamine linked Nucleoside Dimer and Its Incorporation into Antisense Sequences", J. Am. Chem. Soc., 1992, 114, 4006-4007			
FH	Wang, H. et al., "Solid Phase Synt Tetrahedron Letts., 1991, 32, 7385		nucleotide Analogues",	
* FI	Ausubel, F.M. et al. (Eds.), Currer Publications, 1989	Ausubel, F.M. et al. (Eds.), Current Protocols in Molecular Biology, Current Publications, 1989		
* FJ	Green and Wuts, Protective Groups in Organic Synthesis,, John Wiley & Sons, New York, 1999			
EXAMINER		DATE CONSIDI	ERED	

^{*}A copy of this reference will not be forwarded to the U.S. Patent and Trademark Office since it is believed to be too voluminous and easily obtainable by the Examiner.



List of Patent and Publications
Cited by Applicant
(Use several sheets if necessary)

U.S. Department of Commerce Patent and Trademark Office

Docket No.	Serial No.
ISIS-4288	09/438,989

Applicant

Yogesh S. Sanghvi et al.

Filing Date
November 12,
1999

Group **2953**

U. S. PATENT DOCUMENTS

Examiner Initial		Document No.	Date	Name	Class	Subclass
	FK	3,687,808	08/29/72	Merigan et al.	195	28
	FL	4,689,320	08/25/87	Kaji	514	44
	FM	4,806,463	02/21/89	Goodchild et al.	435	5
	FN	5,004,810	04/02/91	Draper	536	27
	FO	5,166,195	11/24/92	Ecker	514	44
	FP	5,194,428	03/16/93	Agrawal et al.	514	44
	FQ	5,212,295	05/18/93	Cook	536	26.7
	FR	5,242,906	09/07/93	Pagano et al.	514	44
,	FS	5,248,670	09/28/93	Draper et al.	514	44
	FT	5,442,049	08/15/95	Anderson et al.	536	24.5

FOREIGN PATENT DOCUMENTS

Examiner Initial		Document No.	Date	Country	Translation YES NO
	FU	WO 94/08003	04/14/94	PCT	X
	FV	WO 99/05160	02/04/99	PCT	X
	FW	WO 89/12060	12/14/89	PCT	X
	FX	WO 90/15065	12/13/90	PCT	X
	FY	WO 91/08213	06/13/91	PCT	X
	FZ	WO 91/10671	07/25/91	PCT	X
EXAMINER			DATE CONSI	DERED	



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List of Patent and Publications Cited by Applicant (Use several sheets if necessary)

U.S. Department of Commerce Patent and Trademark Office

	Serial No.
ISIS-4288	09/438,989

Applicant

Yogesh S. Sanghvi et al.

Filing Date
November 12,
1999

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U. S. PATENT DOCUMENTS

Examiner Initial		Document No.	Date	Name	Class	Subclass
***	GA	5,457,189	10/10/95	Crooke et al.	536	24.5
	GB	5,489,677	02/06/96	Sanghvi et al.	536	22.1
	GC	5,514,577	05/07/96	Draper et al.	435	238
	GD	5,514,788	05/07/96	Bennett et al.	536	23.1
	GE	5,523,389	06/04/96	Ecker et al.	536	23.1
	GF	5,580,767	12/03/96	Cowsert et al.	435	172.3
	GG	5,582,972	12/10/96	Lima et al.	435	6
	GH	5,582,986	12/10/96	Monia et al.	435	6
	GI	5,587,361	12/24/96	Cook et al.	514	44
-	GJ	5,591,600	01/07/97	Ecker	435	69.1

FOREIGN PATENT DOCUMENTS

Examiner Initial		Document No.	Date	Country	Translation YES NO
	GK	WO 91/15500	10/17/91	PCT	X.
	GL	WO 91/18997	12/12/91	PCT	X
	GM	WO 92/02258	02/20/92	PCT	X
	GN	WO 92/03568	03/05/92	PCT	X
	GO	WO 92/05186	04/02/92	PCT	X
EXAMINE	R			DATE CONSI	DERED



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& TRAITEMENT	Form 1	PTO-1449 Modif	ied	Docket No. ISIS-4288	Serial No 09/438,9		
List of Patent and Publications Cited by Applicant (Use several sheets if necessary) U.S. Department of Commerce Patent and Trademark Office				Applicant Yogesh S. Sanghv	Applicant Yogesh S. Sanghvi et al.		
				Filing Date November 12, 1999	Group 2953		
		U. S	S. PATENT DO	CUMENTS			
Examiner Initial		Document No.	Date	Name	Class	Subclass	
	GP	5,591,623	01/07/97	Bennett et al.	435	240.2	
	GQ	5,591,720	01/07/97	Anderson et al.	514	44	
	GR	5,599,797	02/04/97	Cook et al.	514	44	
	GS	5,607,923	03/04/97	Cook et al.	514	44	
	GT	5,620,963	04/15/97	Cook et al.	514	44	
	GU	5,658,891	08/19/97	Draper et al.	514	44	
· ·	GV	5,661,134	08/26/97	Cook et al.	514	44	
	GW	5,681,747	10/28/97	Boggs et al.	435	375	
	GX	5,681,944	10/28/97	Crooke et al.	536	24.5	
	GY	5,691,461	11/25/97	Ecker et al.	536	24.32	
		FORE	IGN PATENT	DOCUMENTS			
Examiner Initial		Document No.	Date	Country	YES	ranslation NO	
	GZ	WO 92/19637	11/12/92	PCT	X		
	НА	WO 92/20822	11/26/92	PCT	X		
	НВ	WO 92/20823	11/26/92	PCT	X		
	нс	WO 93/07883	04/29/93	PCT	X		
	HD	0 216 860 B1	10/28/92	EPO	X		
EXAMINE	ER			DATE CONSID	ERED		

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4 TRATEMEN		PTO-1449 Modif	fied	Docket No. ISIS-4288	Serial No. 09/438,989		
	List of Patent and Publications Cited by Applicant (Use several sheets if necessary)			Applicant Yogesh S. Sanghvi et al.			
		epartment of Comme and Trademark Offi		Filing Date November 12, 1999	Group 2953		
		U.	S. PATENT D	OCUMENTS			
Examiner Initial		Document No.					
	HE	4,415,732	11/15/83	Caruthers et al.	536	27	
	HF	4,458,066	07/03/84	Caruthers et al.	536	27	
	HG	4,469,863	09/04/84	Ts'o et al.	536	27	
	нн	4,476,301	10/09/84	Imbach et al.	536	27	
· · · · · · · · · · · · · · · · · · ·	HI	4,500,707	02/19/85	Caruthers et al.	536	27	
	нј	4,668,777	05/26/89	Caruthers et al.	536	27	
	нк	4,725,677	02/16/88	Köster et al.	536	27	
	HL	4,816,571	03/28/89	Andrus et al.	536	27	
	НМ	4,973,679	11/27/90	Caruthers et al.	536	27	
	HN	5,023,243	06/11/91	Tullis	514	44	
	но	5,034,506	07/23/91	Summerton et al.	528	391	
	НР	5,132,418	07/21/92	Caruthers et al.	536	27	
		FOR	EIGN PATEN	T DOCUMENTS			
Examiner Initial Document No.		Document No.	Date	Country	YES	ranslation NO	
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DATE CONSIDERED

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	C	Patent and Publicati Cited by Applicant veral sheets if necess		Applicant Yogesh S. Sanghvi et al.			
		epartment of Commo and Trademark Off		Filing Date Group November 12, 2953 1999			
		U.	S. PATENT D	OCUMENTS			
Examiner Initial		Document No.	Date	Name	Class	Subclass	
	HQ	Re. 34,069	09/15/92	Köster et al.	536	27	
	HR	5,166,315	11/24/92	Summerton et al.	528	406	
	HS	5,177,196	01/05/93	Meyer, Jr. et al.	536	22.1	
	НТ	5,185,444	02/09/93	Summerton et al.	544	81	
	HU	5,188,897	2/23/93	Suhadolnik et al.	428	402.2	
	HV	5,214,134	05/25/93	Weis et al.	536	25.3	
	HW	5,216,141	06/01/93	Benner	536	27.13	
	HX	5,235,033	08/10/93	Summerton et al.	528	391	
	HY	5,264,423	11/23/93	Cohen et al.	514	44	
	HZ	5,264,562	11/23/93	Matteucci	536	23.1	
	IA	5,264,564	11/23/93	Matteucci	536	23.1	
	IB	5,276,019	01/04/94	Cohen et al.	514	44	
		FOR	EIGN PATEN	T DOCUMENTS			
Examiner Initial			Date	Country	YES	ranslation NO	
EXAMINE	ER			DATE CONSIDE	RED		



4 TRATEMENT	Form	PTO-1449 Modif	ĩed	Docket No. ISIS-4288	Serial No 09/438,98		
	C	Patent and Publication Cited by Applicant weral sheets if necess		Applicant Yogesh S. Sanghvi et al.			
U.S. Department of Commerce Patent and Trademark Office				Filing Date November 12, 1999	Group 2953		
		U.	S. PATENT D	OCUMENTS			
Examiner Initial		Document No.	Date	Name	Class	Subclass	
	IC	5,278,302	01/11/94	Caruthers et al.	536	24.5	
	ID	5,286,717	02/15/94	Cohen et al.	514	44	
	IE	5,321,131	06/14/94	Agrawal et al.	536	25.34	
	IF	5,399,676	03/21/95	Froehler	536	23.1	
	IG	5,405,938	04/11/95	Summerton et al.	528	406	
	IH	5,405,939	04/11/95	Suhadolnik et al.	530	322	
	II	5,434,257	08/18/95	Matteucci et al.	536	24.3	
	IJ	5,453,496	09/26/95	Caruthers et al.	536	24.5	
	IK	5,455,233	10/03/95	Spielvogel et al.	514	44	
· · · · · · · · · · · · · · · · · · ·	IL	5,466,677	11/14/95	Baxter et al.	514	44	
	IM	5,470,967	11/28/95	Huie et al.	536	24.3	
	IN	5,476,925	12/19/95	Letsinger et al.	536	23.1	
· · · · · · · · · · · · · · · · · · ·		FOR	EIGN PATEN	T DOCUMENTS			
Examiner Initial	1 I		Country	YES T	ranslation- NO		
EXAMINI	ER			DATE CONSIDE	CRED		



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	(Patent and Publicati Cited by Applicant veral sheets if necess		Applicant Yogesh S. Sanghvi e	Applicant Yogesh S. Sanghvi et al.			
U.S. Department of Commerce Patent and Trademark Office				Filing Date November 12, 1999	Group 2953			
		U.	S. PATENT D	OCUMENTS				
Examiner Initial		Document No.	Date	Name	Class	Subclass		
	Ю	5,519,126	05/21/96	Hecht	536	24.3		
	IP .	5,536,821	07/16/96	Agrawal et al.	536	22.1		
	IQ	5,541,306	07/30/96	Agrawal et al.	536	22.1		
	IR	5,541,307	07/30/96	Cook et al.	536	23.1		
	IS	5,550,111	08/27/96	Suhadolnik et al.	514	44		
	IT	5,561,225	10/01/96	Maddry et al.	536	23.1		
	IU	5,563,253	10/08/96	Agrawal et al.	536	22.1		
	IV	5,571,799	11/05/96	Tkachuk et al.	514	47		
	IW	5,596,086	01/21/97	Matteucci et al.	536	22.1		
	IX	5,602,240	02/11/97	De Mesmaeker et al.	536	23.1		
	IY	5,608,046	03/04/97	Cook et al.	536	23.1		
	IZ	5,610,289	03/11/97	Cook et al.	536	25.34		
		FOR	EIGN PATEN	T DOCUMENTS				
Examiner Initial Document No. Date		Country	YES Tr	anslation NO				
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		U.	S. PATENT DO	CUMENTS			
Examiner Initial		Document No.	Date	Name	Class Subclas		
-	JA	5,618,704	04/08/97	Sanghvi et al.	435	91.5	
	JB	5,623,070	04/22/97	Cook et al.	536	27.6	
	JC	5,625,050	04/29/97	Beaton et al.	536	24.1	
	JD	5,633,360	05/27/97	Bischofberger et al.	536	22.1	
<u> </u>	JE	5,663,312	09/02/97	Chaturvedula	536	22.1	
	JF	5,670,633	09/23/97	Cook et al.	536	23.1	
	JG	5,677,437	10/14/97	Teng et al.	536	23.1	
-	JН	5,677,439	10/14/97	Weis et al.	536	23.1	
	Л	4,845,205	07/04/89	Huynh Dinh et al.	536	28	
	JJ	4,981,957	01/01/91	Lebleu et al.	536	27	
	JK	5,118,800	06/02/92	Smith et al.	536	23	
	JL	5,124,047	06/23/92	Quach, et al.	210	699	
		FOR	EIGN PATENT	DOCUMENTS			
Examiner Initial	•	Document No.	Date	Country	YES T	ranslation NO	

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U. S. PATENT DOCUMENTS

Examiner Initial		Document No.	Date	Name	Class	Subclass
	JM	5,130,302	07/14/92	Spielvogel et al.	514	45
	JN	5,134,066	07/28/92	Rogers et al.	435	91
	JO	5,138,045	08/11/92	Cook et al.	536	27
- Marie	JP	5,175,273	12/29/92	Bischofberger et al.	536	27
	JQ	5,218,105	06/08/93	Cook et al.	536	25.31
	JR	5,223,618	06/29/93	Cook et al.	544	276
	JS	5,264,562	11/23/93	Matteucci		
	JT	5,319,080	06/07/94	Leumann	536	27.1
	JU	5,359,044	10/25/94	Cook et al.	536	23.1
7.7	JV	5,367,066	11/22/94	Urdea et al.	536	24.3
	JW	5,378,825	01/03/95	Cook et al.	536	25.34
	JX	5,386,023	01/31/95	Sanghvi et al.	536	25.3
 	JY	5,393,878	02/28/95	Leumann	536	28.2
	JZ	5,432,272	07/11/95	Benner	536	25.3
-	KA	5,446,137	08/29/95	Maag et al.	536	23.1
	КВ	5,457,187	10/10/95	Gmeiner et al.	536	25.5
	KC	5,457,191	10/10/95	Cook et al.	536	27.13
	KD	5,459,255	10/17/95	Cook et al.	536	27.13
	KE	5,466,786	11/14/95	Buhr et al.	536	26.26
	KF	5,484,908	01/16/96	Froehler et al.	536	24.31
	KG	5,502,177	03/26/96	Matteucci et al.	536	2606
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U. S. PATENT DOCUMENTS

Examiner Initial		Document No.	Date	Name	Class	Subclass
***	КН	5,506,351	04/09/96	McGee	536	55.3
	KI	5,514,785	05/07/96	Van Ness et al.	536	22.1
	KJ	5,519,134	05/21/96	Acevedo et al.	544	243
	КК	5,525,711	06/11/96	Hawkins et al.	536	22.1
	KL	5,543,507	08/06/96	Cook et al.	536	23.1
	KM	5,552,540	09/03/96	Haralambidis	536	25.34
	KN	5,567,811	10/22/96	Misiura et al.	536	25.34
	ко	5,571,902	11/05/96	Ravikumar et al.	536	22.1
	KP	5,576,427	11/19/96	Cook et al.	536	23.1
, 14 J. H. A.	KQ	5,578,718	11/26/96	Cook et al.	536	27.21
	KR	5,587,469	12/24/96	Cook et al.	536	23.1
	KS	5,591,722	01/07/97	Montgomery et al.	514	45
	KT	5,594,121	01/14/97	Froehler et al.	536	23.5
	KU	5,596,086	01/21/97	Matteucci, et al.	536	22.1
	KV	5,596,091	01/21/97	Switzer	536	24.5
	KW	5,597,909	01/28/97	Urdea et al.	536	24.3
	KX	5,602,000	02/11/97	Hyman	435	91.1
	KY	5,610,300	03/11/97	Altmann et al.	544	244
	KZ	5,614,617	03/25/97	Cook et al.	536	23.1
	LA	5,623,065	04/22/97	Cook et al.	536	23.1
	LB	5,627,053	05/06/97	Usman et al.	435	91.1
EXAMINI	ER			DATE CONSIDE	RED	



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U. S. PATENT DOCUMENTS

Examiner Initial		Document No.	Date	Name	Class	Subclass
	LC	5,639,873	06/17/97	Barascut et al.	536	25.3
	LD	5,646,265	07/08/97	McGee	536	25.34
	LE	5,658,873	08/19/97	Bertsch-Frank et al.	510	375
	LF	5,681,941	10/28/97	Cook et al.	536	23.1
	LG	5,700,920	12/23/97	Altmann et al.	536	221
	LH	5,817,781	10/06/98	Swaminathan et al.	536	22.1
	LI	5,859,221	01/12/99	Cook et al.	536	23.1
**	LJ	07/806,710	12/12/91	Jones, et al.		
**	LK	07/990,848	12/11/92	Jones, et al.		
**	LL	08/398,901	03/06/95	Cook et al.		
**	LM	08/762,488	12/10/96	Cook, et al.		
**	LN	08/837,201	03/14/97	Dean et al.		
**	LO	08/910,629	08/13/97	McKay et al.		
**	LP	09/009,490	01/20/98	Bennett et al.		
**	LQ	09/016,520	01/30/98	Cook et al.		
**	LR	09/044,506	03/19/98	Bennett et al.		
**	LS	09/062,416	04/17/98	Bennett et al.		
EXAMINE	ER			DATE CONSIDER	RED	

^{**}Pursuant to 37 C.F.R. 1.98(a)(2)(iii) no copy of a U.S. patent application need be included with an Information Disclosure Statement filed under 37 C.F.R. 1.97.

VI TRAVELLAS	List of Patent and Publications Cited by Applicant (Use several sheets if necessary)			Docket No. ISIS-4288			
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		U.	S. PATENT D	OCUMENTS			
Examiner Initial	Document No. Date		Name	Class	Subclass		
**	LT	09/115,043	07/14/98	Manoharan et al.			
**	LU	09/123,108	07/27/98	Manoharan et al.			
**	LV	09/130,973	08/07/98	Manoharan et al.			
**	LW	09/344,260	06/25/99	Manoharan			
**	LX	09/370,541	08/09/99	Manoharan, et al.			
**	LY	09/349,040	07/07/99	Manoharan et al.			
**	LZ	09/378,568	08/19/99	Manoharan et al.			
		FOR	EIGN PATEN	T DOCUMENTS			
Examiner Initial		Document No.	Date	Country	YES Ti	ranslation NO	
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^{**}Pursuant to 37 C.F.R. 1.98(a)(2)(iii) no copy of a U.S. patent application need be included with an Information Disclosure Statement filed under 37 C.F.R. 1.97.